Veterinary Immunology and Immunopathology 128 (2009) 24–29

Contents lists available at ScienceDirect

Veterinary Immunology and Immunopathology

journal homepage: www.elsevier.com/locate/vetimm

Research paper

A current perspective on availability of tools, resources and networks for veterinary immunology

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ARTICLE INFO

Keywords:
Antibodies
Cytokines
Veterinary
Reagents
Databases

ABSTRACT

There are many diseases of fish, livestock and companion animals that impact negatively on animal health, welfare and productivity and for which there are no effective vaccines. The development of new vaccines is reliant on the availability of well-characterised immunological tools and reagents to understand host–pathogen interactions and identify protective immune responses. Veterinary immunology has always lagged behind mouse and human immunology in terms of development and availability of tools and reagents. However, several initiatives are underway to address this. The Veterinary Immunology Committee (VIC) Toolkit was initiated 6 years ago at the sixth International Veterinary Immunology Symposium (IVIS) in Uppsala and in the intervening period there have been several notable developments that have advanced reagent development and information exchange. This review will discuss advances in veterinary reagent development, networks, databases and commercial availability with particular reference to the second VIC Toolkit workshop held at the eighth IVIS in Ouro Preto, Brazil on the 15th of August 2007.

1. Introduction

The development of immunological tools and resources is essential for underpinning hypothesis-driven research into infectious, oncogenic or immune system-based diseases of humans and animals. The animal model of choice for the vast majority of researchers working on human diseases is the mouse. The focus on this model has resulted in the development of congenic mice, gene knock-out mice, transgenic mice and also in the development of an extensive range of murine-specific immunological reagents and techniques. Without these resources we would not have the advanced understanding of the organisation, structure and function of the immune system that exists today. Equally, there would not be the wherewithal to analyse immune responses to infectious agents and tumours, or to investigate diseases of immune dysregulation such as autoimmunity, immunodeficiencies and allergies.

The investment in basic immunology research in mice has been justified by the success in applying the results to prevent and control disease in humans. The immune system has evolved to protect the host against disease and since host species live in different environments the pathogens encountered will also differ. Thus it is logical to expect that individual species will rely on different elements of the immune system that may vary across species even though most fundamental aspects of host protection are evolutionarily conserved. For example, swine responses to most cytokines are similar to human and cattle; however, their response to IL-12 is not correlated with up-regulation of the expression of IL-12β2 receptor thus potentially altering Th1 pathways (Solano-Aguilar et al., 2002). As another example, the Th2 bias and modulation of maternal T cell immunity widely

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0165-2427/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.vetimm.2008.10.291

reported in pregnant humans and mice does not appear to occur in sheep, possibly a reflection of the different types of placentation in these species (Wattegedera et al., 2008). These studies were dependent on appropriate immunological probes, assays and reagents for the species in question, highlighting the information to be gleaned from comparative immunology. At the time of writing, two reports on mouse IL-35 have recently been published (Collison et al., 2007; Neidbala et al., 2007), demonstrating that immunology in many veterinary species still lags behind that in mice and requires further investment.

There are relatively lower financial returns for diagnostics, prophylactics and therapeutics in the veterinary sector compared to human medicine. Nevertheless, infectious diseases of livestock and companion animals negatively impact on animal health and welfare and can be of economic importance. In certain diseases there is also a direct risk to human health via transmission of zoonotic pathogens, be they viral, bacterial or parasitic (Merianos, 2007). Moreover, animals serve as a major source of food and the Foot and Mouth Disease Virus (FMDV) outbreak in the UK in 2001 demonstrated how vulnerable the food supply can be to infectious diseases and underlined the need for marker vaccines.

There are considerable ongoing efforts globally to develop effective, safe and affordable vaccines to control animal diseases. Empirical vaccine design is now largely in the past and the next generation of vaccines requires a detailed understanding of the protective host response elements and immune regulation if they are to be delivered effectively with maximum effect. Moreover, there are increasing regulatory requirements from licensing bodies to demonstrate that a new vaccine is capable of inducing a correlate of protection for the disease it is designed to prevent. It is a goal to do so in the target species and not in a model. Thus, the necessity of an expanded immune toolkit for each veterinary species.

The development of tools and resources to conduct high-quality immunology research in different vertebrate species is an ongoing process. This review discusses the various initiatives and networks geared towards the production and accessibility of reagents and resources to the veterinary immunology research community, focussing on the Veterinary Immunology Committee (VIC) Toolkit Workshop held in Ouro Preto, Brazil in August 2007.

2. The establishment of the VIC Toolkit

The concept of a VIC Toolkit took shape at the sixth International Veterinary Immunology Symposium (IVIS) in Uppsala, Sweden held in July 2001. VIC is one of the five committees belonging to the International Union of Immunological Societies (IUIS; http://www.iuisonline.org/) and one of its goals is to support pre-symposium workshops at IVIS. These workshops tend to focus on reagents, technologies and emerging topics of interest to veterinary immunologists that might not otherwise be covered in the main symposium.

One of the workshops in Uppsala was on ruminant immunology and issues relating to the availability of reagents and technologies for research (Entrican, 2002). The expectation at the time was that around 30 delegates would attend the workshop. However, the level of interest became apparent when the session had to move to a new room to accommodate almost 200 delegates. Joan Lunney was the then Chair of VIC and in accordance with the objectives of VIC to set up subcommittees, Joan proposed that a VIC Toolkit Committee be set up alongside the existing Comparative Immunoglobulin Workshop (CIgW), Cross-reactive Antibody Workshop (HLDA) and Comparative MHC Nomenclature Committee (ISAG) to reflect the interest in this area.

VIC ratified this proposal and Gary Entrican and Victor Rutten were subsequently appointed as co-chairs to develop a VIC Toolkit Committee in consultation with Dr. Lunney. That group of individuals established the remit and objectives for the VIC Toolkit (Fig. 1). It was agreed that the committee should cover nine groups and four discipline/technology areas, and include committee members who have appropriate expertise/knowledge in each species or area from around the globe. Those species to be covered include fish, poultry, horses, ruminants (principally sheep and cattle), dogs, cats, swine and wildlife species. The committee members are to include delegates from the other VIC Workshops/Committees (HLDA, ISAG, CIgW) to ensure good communication between these subgroups that share common interests.

There is also good cross-representation from veterinary committees of learned Immunological Societies such as the European Veterinary Immunology Group (EVIG; http://www.izw-berlin.de/evig/Main.html) run under the auspices of the European Federation of Immunological Societies (EFIS), Comparative Veterinary Immunology Group (CVIG; http://www.iah.bbsrc.ac.uk/cvig/) which is an Affinity Group of the British Society for Immunology (BSI), and the American Association of Veterinary Immunologists (AAVI; http://www.theaavi.org/) which runs meetings with the American College of Veterinary Microbiology as a prelude to and during the Conference of Research Workers in Animal Diseases (CRWAD) and is a sister society of the American Association of Immunologists (AAI). The VIC Toolkit Committee structure was still developing at the time of the seventh IVIS in Quebec City in 2004 where the first VIC Toolkit Workshop was held. The discussions during and after that workshop helped shape the final structure of VIC Toolkit Committee which was put in place soon afterwards and is shown in Fig. 2.

VIC Toolkit

Remit:
To provide a global network for veterinary reagent availability and facilitate information exchange

Objectives:
1. To advise on priorities for reagent development and avoid unnecessary duplication of effort;
2. Support international communication and collaboration;
3. Explore mechanisms for managing orphan reagents;
4. Engage with industry to encourage technology transfer thereby increasing the commercial availability of veterinary immunology reagents.

Fig. 1. Remit and objectives of VIC Toolkit.

VIC Toolkit Committee

Chairs:
Gary Entrican (UK), Victor Rutten (Netherlands)

Species:

Aquatic:	Chris Secombes (UK)
Avian:	Pete Kaiser (UK), Bernd Kaspers (Germany)
Bovine:	Cynthia Baldwin (USA), Jayne Hope (UK)
Canine:	Stuart Carter (UK)
Equine:	Paul Lunn (USA), David Horohov (USA)
Feline:	Mary Tompkins (USA), Thomas Vahlenkamp (Germany)
Ovine:	Els Meeusen (Australia), Peter Hansen (USA)
Porcine:	Harry Dawson (USA), Francisco Javier Dominguez (Spain)
Wildlife:	Falko Steinbach (UK), Jacques Godfroid (South Africa)

Areas:

VIC/HLDA:	Armin Saalmuller (Austria), Bent Aasted (Sweden)
VIC/ISAG:	Shirley Ellis (UK), Lorna Kennedy (UK)
VIC/CIgW:	John Butler (USA), Imre Kaskovics (Hungary)
Microarrays:	Dirk Werling (UK), Tracey Coffey (UK)

Fig. 2. Structure and organisation of VIC Toolkit Committee.

This committee underpins delivery on the objectives of VIC Toolkit, serving as an international communication network that complements the VetImm email forum (https://list.umass.edu/mailman/listinfo/vetimm) that was conceived at the fourth IVIS in Davis, California in 1998. The VIC Workshops at IVIS also underpin the Toolkit objectives by providing an opportunity for the veterinary immunology research community to discuss reagent needs and debate mechanisms for advancing reagent development and availability. The second VIC Toolkit Workshop in Ouro Preto included presentations on major consortia projects geared towards veterinary reagent development, database construction and concluded with an open discussion on the key points raised during the session. Posters linked to the workshop were presented collectively at the main IVIS.

3. Consortium projects

3.1. BBSRC/RERAD Toolbox

The Toolbox is a ground-breaking initiative, jointly funded for 4 years by the Biotechnology and Biological Sciences Research Council (BBSRC) and the Scottish Government, Rural and Environment Research and Analysis Directorate (RERAD) in the UK in 2004. The aims of the Toolbox are to develop immunological reagents and resources for five veterinary species (cattle, sheep, pigs, chickens and horses) at three research institutes (Institute for Animal Health [IAH], Animal Health Trust [AHT] and Moredun Research Institute [MRI]). The driving force behind the concept of an Immunological Toolbox was Professor Jim Kaufman (IAH), who presented an update on the Toolbox at the VIC Toolkit Workshop. It was clear from that presentation that considerable progress has been made since 2004, when Professor Kaufman first reported the Toolbox as a nascent project at the VIC Workshop in Quebec City.

Details of the organisation, aims, objectives and achievements of the BBSRC/RERAD Toolbox, including a virtual poster room displaying the Toolbox reagent posters presented at the eighth IVIS in Ouro Preto, can be found at http://www.immunologicaltoolbox.co.uk/. An underlying ethos of the competitively funded Toolbox Consortium is deriving added value from funding posts at three Veterinary Research Institutes that have existing infrastructure, expertise and commitment to developing immunological reagents. The Consortium also derives added value from the sharing of knowledge and resources, to advance reagent development and avoid duplication of effort. This requires good communication on a global basis and an awareness of priorities and developments in other organisations. As discussed below, there are several mechanisms in place to facilitate effective communication between different laboratories around the world.

3.2. USDA/VIRN

The Veterinary Immune Reagent Network (VIRN) was approved for funding by the United States Department of Agriculture (USDA) in 2005 and the project launched in February 2006. The project addresses the needs of six species/groups (catfish, horses, ruminants, pigs, poultry and trout) with dedicated locations for recombinant protein expression and monoclonal antibody production. The project co-ordinator is Cynthia Baldwin (University of Massachusetts, Amherst), who reviewed progress at the VIC Toolkit Workshop. As with the Toolbox, full details of USDA/VIRN can be found at: http://www.vetimm.org/.

The structure of USDA/VIRN differs from the BBSRC/RERAD Toolbox in that the partners are based in a wide variety of academic, government and commercial organisations (University of Massachusetts, University of Mississippi, University of Kentucky, Cornell University, USDA-ARS-BARC Maryland, USGS-Western Fisheries Research Center and Kingfisher Biotech). Although the structure differs, there are common target species between the UK and US consortia. The two consortia avoid duplication of effort and maximise their progress by frequent communication via their Advisory Boards. Jim Kaufman and Gary Entrican from the BBSRC/RERAD Toolbox are on the USDA/VIRN Advisory Board, with a reciprocal arrangement with Cynthia Baldwin being the UK Toolbox board. There are also several members of VIC Toolkit Committee involved in the research activities or the Advisory Boards of the consortia, creating an integrated international network for information exchange.

3.3. Past and present research efforts

Past effort sponsored by the IUIS VIC included numerous international workshops to compare the basic mAb reagents produced internationally for specificity for CD antigens in important veterinary species. There were series of formal international CD workshops where reagents were exchanged and evaluated between laboratories by the swine, horse and ruminant communities (Haverson et al., 2001; Naessens and Hopkins, 1996; Lunn et al., 1995) with less extensive exchanges by the avian community (Ratcliffe et al., 1993). These efforts were extended by the CIgW to the area of reagents specific for immunoglobulins (Igs) and Fc receptors (Butler and Howard, 2002). More recently a formal test of anti-human

CD mAb for reactivity against molecules from a broad array of species was coordinated with the Animal Homologue Section of HLDA8 workshop (Saalmüller et al., 2005; Saalmüller and Aasted, 2007).

There have been, and are, many groups in several other countries working on veterinary immunological reagent development. Many of the ruminant phenotypic and cytokine reagents currently available through commercial sources were derived from work conducted over the past 25 years at the Centre for Animal Biotechnology (CAB; http://www.cab.unimelb.edu.au/) and at the Commonwealth Scientific and Industrial Research Organisation in Parkville (CSIRO; http://csiro.au/), both in Australia, and at the International Livestock Research Institute, in Nairobi (ILRI; http://www.ilri.org/). Some of these organisations have undergone structural changes and are not developing reagents to the extent that they had done in the past. However, there are many other organisations and universities such as University of Utrecht (http://www.vet.uu.nl/; see also Section 5) and Washington State University (http://www.vetmed.wsu.edu/) that have also commercialised their reagents and continue to develop reagents. This list is certainly not exclusive since almost everyone involved in veterinary immunology is developing tools, reagent and resources to some extent.

Table 1
Websites of research consortia, veterinary reagent databases, research consortia, and commercial sources of reagents and tools.

1. Research consortia
   http://www.immunologicaltoolbox.co.uk/
   http://www.vetimm.org/

2. Reagent databases and resources
   http://www.ars.usda.gov/Services/docs.htm?docid=6065
   http://www3.niaid.nih.gov/research/resources/ri
   http://www.ca.uky.edu/gluck/HorohovDW_EIR.asp
   http://eis.bris.ac.uk/~lvkh/welpig.htm
   http://www.animal.ufl.edu/hansen/Immunology_resources/VETIMMUNOLRESOURCES.htm
   http://www.ebi.ac.uk/imgt/
   http://www.medicine.uiowa.edu/CIgW/
   http://www.ebi.ac.uk/ipd/mhc/
   http://www.cafg.msu.edu/
   http://www.ark-genomics.org/

3. Commercial sources of veterinary immunology reagents
   http://www.kingfisherbiotech.com/
   http://www.cytocen.com/
   http://www.ab-direct.com/index
   http://www.scbt.com/
   http://www.vmrd.com/
   http://www.invitrogen.com/
   http://www.endogen.com/
   http://www.prionics.com/

4. The VetImm list
   https://list.umass.edu/mailman/listinfo/vetimm

4. Databases

Information on gene sequences, molecular probes, recombinant proteins and antibodies for veterinary immunology is rapidly expanding and databases are essential management tools for collating that information in a form that can be easily interrogated. One of the objectives of VIC Toolkit is to devise means of facilitating exchange of information, which includes the provision of links to existing databases. At the VIC Toolkit Workshop in Ouro Preto, Harry Dawson (USDA-ARS, Beltsville) gave an update on the porcine immunology and nutrition resource database he has developed. This database is a remarkable collection of information on around 3000 porcine genes associated with metabolism, disease pathogenesis and immunity including pathogen recognition, cell signalling and lymphocyte development. The database links gene expression with function and also contains information on antibodies, proteins and real-time PCR for studies in swine. The database can be found at: http://www.ars.usda.gov/Services/docs.htm?docid=6065. A list of websites for reagent databases, reagent sources, committees and consortia is provided in Table 1.

Both the BBSRC/RERAD Toolbox and USDA/VIRN are constructing lists and databases of reagent availability, bioassays, and cross-reactivity in their species of interest. These will be publicly accessible online. Ultimately these various databases will be flagged via links on several websites and therefore easily accessible.

A commonly voiced concern regarding websites is the validity of the data contained therein if not supported by reference to peer-review publications. Websites had commonly have disclaimer statements for protection, but providers are likely to do their utmost to ensure that information is as accurate as possible before lodging it. As with all areas of science, there will be degrees of interpretation depending on the nature of the data.

Feedback is to be encouraged since it will expand and strengthen the databases. Citations and examples of reagent applications are very useful. It is also useful if 'negative' data are lodged, for example the failure of antibodies to stain paraffin-embedded sections or to cross-react. Positive controls are of paramount importance in such experiments. However, such information often does not appear in publications and solid negative data are invaluable for informing others that certain routes are not productive to follow. Databases will aim to include negative reactivities for reagents where appropriate.

5. Accessibility and commercialisation of veterinary reagents

Exchange of veterinary immunology reagents has often been conducted on an informal collaborative basis, with individuals who have reagents providing them to those who require them. Such arrangements have both advantages and disadvantages for the parties concerned. Providers produce and ship the materials, both of which are time-consuming and potentially expensive. Moreover, if the shipping is on dry ice to an overseas destination, the paperwork for importation in itself can almost be prohibitive. Additionally, recipients may offer, or be asked, to pay shipping and/or production costs by the provider and are likely to be asked to sign a Material Transfer Agreement (MTA) to protect the provider regarding the use and further distribution of the material. Collectively these factors have changed the way that reagents are exchanged and if a provider does not have the resources or incentive

to distribute reagents to a requisitioner then accessibility to reagents will be compromised. Moreover, as researchers move or retire sets of reagents are becoming "orphaned."

Commercialisation can overcome many of these issues, and although recipients may have to pay more than they would under collaborative arrangements, the advantages for both parties are considerable. Firstly, providers will be relieved of the above demands and will receive a royalty on sales. Secondly, both parties will have the service support and quality assurance of the commercial organisation. Thirdly, reagent accessibility will be determined by an ability to pay for a product, not the discretion of the scientist who developed the reagent.

The commercial cost of reagents does appear to be an issue for some veterinary immunologists. This may be historical, since the widespread, friendly and altruistic exchange of reagents on a no-cost basis among the veterinary community has contributed to a situation where reagents are often expected cheaply or gratis. So where does industry sit within this? The relatively small veterinary immunology research community and the relatively low financial return on veterinary/livestock vaccines (both compared to mouse models/human immunology), the result is that industry appears to be unwilling to fund development of basic veterinary immunology reagents, presumably because profit margins do not justify it.

However, a market does exist as evidenced by companies that have a portfolio of veterinary reagents, although most of these reagents have been acquired from research laboratories. It is therefore essential that grant-awarding bodies, charities and foundations as well as government-sponsored research institutes continue to fund veterinary immunological reagent development, either at individual project or consortium level (with the latter proving very successful). Researchers are fully aware that generation of income through technology transfer and commercialisation of immunological tools is an important goal. Royalties can be re-invested in basic research and work hand-in-hand with the research funding.

The current situation is that industrial partners appear willing to enter into agreements with research organisations/consortia to mutually develop reagents or to market reagents that are already developed under non-exclusive agreements. Spin-out companies are another option. For example, the Utrecht Cytokine Centre/CytoCen was presented at the VIC Toolkit workshop at eighth IVIS by Edwin Tijhaar. The Cytokine Centre is a Division within the Faculty of Veterinary Medicine at University of Utrecht, Netherlands; CytoCen is a commercial venture recently derived from the Cytokine Centre that will commercialise their reagents. The portfolio of products is monoclonal and polyclonal antibodies to a range of cytokines for a number of veterinary species. These antibodies were initially available collaboratively under MTAs, but will now be available on a commercial basis. The US VIRN has included a commercial partner from its original grant application; Kingfisher Biotech is an active partner in USDA/VIRN's production plan.

Researchers have varied, but often challenging opinions regarding the approach that industry currently takes regarding veterinary immunology reagents. It is viewed by some as largely exploitation of existing reagents with little or minimal investment in development. It is worth noting, however, that many and perhaps even most mouse and human reagents marketed by companies are also derived from individual research scientists. However, as more reagents become available and veterinary immunology advances, more work will be conducted resulting in improved disease prevention and control in veterinary species/livestock. In addition, species other than mice can be superior models for human diseases and are very relevant for studying zoonoses. Such broad applications may prove to be financial drivers to strengthen the business case for commercial investment in reagent development.

6. Concluding remarks

Given that the 'easy' veterinary vaccines have already been developed, the next generation of safe, effective and affordable subunit vaccines depend on a detailed understanding of immune responses to pathogens in their natural hosts. Without the ability to identify what constitutes a protective immune response, it is impossible to rationally mimic that protection while constructing a vaccine. The dearth of immunological reagents that are currently available remains a barrier to such studies. However, recent investment in large consortia to develop reagents has generated optimism and it is noticeable that considerable progress has been made on several fronts since the inception of the VIC Toolkit in 2001. It is essential that funding streams remain open because the momentum that has been generated must be maintained. There are still many gaps in capability compared to mouse and human immunology, but veterinary immunology is moving forward with a global impetus. Questions and suggestions on any aspects of veterinary immunology can be posted to the international community on the VetImm list: https://list.umass.edu/mailman/listinfo/vetimm

Conflict of interest

None.

Acknowledgements

The authors thank IUIS-VIC for developing and supporting the VIC Toolkit Initiative. G.E. is funded by the Scottish Government, Rural and Environment Research and Analysis Directorate (RERAD) and supported by the BBSRC/RERAD Toolbox, grant numbers BBS/B/00255, MRI/094/04. J.L. and C.B. are supported by the USDA/VIRN, the National Research Initiative of the USDA Cooperative State Research, Education and Extension Service, grant number 2006-35204-16880.

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